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J. Mitchell Jones MEDLEN & CARROLL, LLP Suite 350 101 Howard Street San Francisco, CA 94105			RIGGINS, PATRICK S	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/759,315	Applicant(s) BLECK ET AL.	
	Examiner Patrick S. Riggins	Art Unit 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 16 January 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-42 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-42 is/are rejected.
- 7) ☒ Claim(s) 39 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 16 January 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

S.O.O.

DETAILED ACTION

Specification

1. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.
2. The disclosure is objected to because of the following informalities: The Description of the Figures should be entitled Brief Description of the Drawings. In this section, Figures 21-25 do not contain reference to parts A-D of Figures 21-22 or parts A-C of Figures 23-25. Page 50, line 29 refers to "IbE" when --IgE-- would appear to have been intended. Page 58 improperly states that the ATCC is located in Rockville, MD. The ATCC has moved and is now located in Manassas, VA.

Appropriate correction is required.

3. The use of the trademarks OAKRIDGE TUBES, INVADER ASSAY SYSTEM, and BLASTICIDIN has been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Objections

4. Claim 39 is objected to because of the following informalities: IbE is not a proper name for an immunoglobulin. Appropriate correction is required.

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5. Applicant is advised that should claim 30 be found allowable, claim 42 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claim 42 is identical to the dependency chain of claim 30 with the exception of the limitations provided by claim 28, wherein the host cells are cultured under conditions that the protein of interest is produced. As this is an inherent step in the purification of protein, there is no patentable distinction between claims 30 and 42.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claim 1 recites the limitation "said plurality of integrating vectors" in line 5. There is insufficient antecedent basis for this limitation in the claim.

9. Claims 12 and 13 are both draw attention to steps 1 and 2 of claim 1 when claim 1 had no steps 1 and 2. The confusion arises because this could necessarily refer to either steps i and ii, or steps a and b.

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10. Claim 19 recites the limitation "said host" in line 1. There is insufficient antecedent basis for this limitation in the claim.

11. Claim 21 recites "signal sequence". The confusion regarding this limitation arises because there is not a clear definition as to what is intended by a "signal sequence". The specification only seems to define this to refer to a "secretion signal sequence", but claim 29 places the limitation that the construct comprise a "secretion signal sequence", thus casting doubt as to the meaning of "signal sequence". This limitation in claim 21 will be read to encompass any sequence that specifically targets a protein to a particular subcellular localization. Additionally, as a signal sequence is an amino acid sequence and a gene is a nucleotide sequence. Therefore this wording of the claim is vague and indefinite. To recite --operably linked to a segment encoding a signal sequence-- would be remedial.

12. Claim 29 recites the limitations "said integrating vector" and "said exogenous gene". There is insufficient antecedent basis for these limitations in the claim. Additionally, as above, the retroviral vector itself does not comprise a secretion signal sequence. Reciting --comprises a segment encoding a secretion signal sequence-- would be remedial.

13. Claims 32-34 recite the limitation "said host cell". This is an insufficient limitation as this could refer to the clonally selected host cell of claims 27 and 28, or any of three types of host cell from claim 1. In the interest of compact prosecution, "said host cell" in this context will be assumed to refer to the clonally selected host cells of claims 27 and 28. If this is indeed the intention, reciting --said clonally selected host cells-- would be remedial.

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14. Claim 42 recites “said plurality of integrating vectors” and “repeating steps 1) and 2)”.

Both recitations lack antecedent basis and the latter is particularly unclear as this could be referring to steps i and ii or steps a and b.

15. As claims 2-11, 14-18, 20, 22-28, 30-31, and 35-41 all ultimately depend from claim 1 which is itself vague and indefinite, they too are held to be vague and indefinite.

Claim Rejections - 35 USC § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

17. Claims 1-5, 10, 18, 20-21, and 41 are rejected under 35 U.S.C. 102(b) as being anticipated by Inaba (J. Surg Res. 78:31-26 (1998), newly cited). The claims are drawn to a method of transducing host cells where host cells are contacted repeatedly with a retroviral vector encoding a gene of interest, up to 6 times, resulting in host cells comprising multiple integrated vectors. The retroviral vector may comprise elements from MoMLV and the gene of interest may be linked to an exogenous promoter or a signal sequence. Also claimed is a host cell produced by the method of claim 1.

18. Inaba discloses (see Materials and Methods, and Figure 1) a method for transducing endothelial cells comprising contacting the endothelial cells with viral supernatant 4-6 times over a 10-14 day period. The vector comprised β -D-galactosidase comprising a nuclear localization signal, which was expressed under the control of the MoMLV LTR. Though not specifically

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disclosed, this transduction protocol would necessarily lead to the integration of multiple retroviral vectors. Figure 2 shows that Inaba also produces the product host cells.

19. Claims 1, 18, 20-21, 27-31, and 40-42 are rejected under 35 U.S.C. 102(b) as being anticipated by Primus (Cancer Res. 53:3355-3361 (1993), newly cited). The claims are drawn to a method for transducing host cells by contacting a host cell with retroviral vectors encoding a gene of interest, repeating the contacting where different vectors encoding distinct genes of interest, such that host cells comprising multiple integrated retroviral vectors. The vector can comprise MoMLV elements and the gene of interest can be linked to an exogenous promoter or a secretion signal sequence. The method can further comprise clonally selecting the transduced host cells, culturing the clonally selected cells to allow for production of the protein of interest and subsequent purification of the protein of interest. The culture conditions can be Petri dish cultures. The host cell produced by the method of claim 1 is also claimed.

20. Primus discloses (see the Abstract and Materials and Methods) a method of expressing the D612 monoclonal antibody in colon carcinoma cells, where the light chain, expressed from the vector pLNCXII, which contains MoMLV LTRs, is first introduced in to the cells, followed by the heavy chain in a sequential manner. The transduced cells were clonally selected after drug selection. As the product antibody was both secreted and expressed on the cell surface, the expressed chains necessarily were linked to secretion signals (see Figures 2-4). The fully functional IgG was purified from the cells.

21. Claims 1, 18, 20-21, 27-31, and 40-42 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,637,483 (hereinafter Dranoff, newly cited). The claims are drawn to the subject matter as described in paragraph 19 above. Dranoff discloses (see Examples

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1-3 and 8) the production of B16 melanoma cells that express IL-2 and GM-CSF additionally with either IL-4 or γ -interferon, through serial retroviral infection of the cells with viruses encoding the different cytokines (Example 8). The vectors comprise MoMLV gag sequences and the secreted cytokines are under the control of the MoMLV LTR (Example 1). The last line of Example 3 states that the transduced cells were clonally selected. To perform the cytokine assays of Example 2 the cytokines were isolated. The cells were grown in standard culture conditions equivalent to Petri dish growth. In performing these methods, the host cells were produced.

22. Claim 41 is rejected under 35 U.S.C. 102(b) as being anticipated by Mathor (Proc. Natl. Acad. Sci. USA 93:10371-1-376 (1996), newly cited. Claim 41 is drawn to a host cell comprising multiple integrated retroviral vectors created by the method of claim 1. Although the method of claim 1 requires repeated transduction cycles, a host cell with multiple integrations produced in this way would be undistinguishable from cells comprising multiple integrated retroviral vectors produced any other way. Mathor discloses clones of cells containing up to 15 retroviral integrations (see Table 1).

Claim Rejections - 35 USC § 103

23. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

24. Claims 1-11, 18-21, 27-34, and 41-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mathor in view of Inaba. Mathor discloses a method for transducing human

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keratinocytes with retroviral vectors based off of LXS_N, which utilizes the MoMLV LTR as its promoter. The multiplicity of infection was at least 100, as the producer cells produced 10^6 colony-forming units per ml. The keratinocytes were seeded at 5×10^3 cells per cm^2 , which even allowing for doubling of the cells is at least an moi of 100 (Materials and Methods). The cells were isolated clonally and it was determined that up to 15 integrations were present in independent clones and that over 1 pg/cell/day of hIL-6 was produced and isolated for measurement of IL-6 levels. The protein was produced in Petri dish cultures. Mathor had the understanding that “there was very good correlation between the number of proviral integrations (from 1 to 15) and the hIL-6 secretion rate (150-1140 ng/ 10^6 cells/day)” (last line of the first full paragraph of page 10375, column 1). Thus, to achieve a higher level of protein production, Mathor would desire cells with a greater number of integrants. Additionally, as described in paragraph 22, Mathor discloses the cells of claim 41. Mathor does not teach repeating the transduction steps.

25. Inaba teaches a transduction protocol involving 4-6 serial exposures of the cells to be transduced to the retroviral supernatant over a 10-14 day period. Inaba performs this serial transduction protocol for the purpose of increasing the percentage of cells transduced. The skilled artisan would clearly have recognized that a serial transduction protocol would have also led to superinfection of cells that had previously been infected, thus leading to a greater number of integrants, and as determined by Mathor, consequently, greater production levels of the protein of interest. The skilled artisan would have had a reasonable expectation of success, because the obstacle to standard superinfection is interference where the expressed envelope proteins from the integrated provirus, interfere with the viral receptors on the cell surface. As the

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retroviral vectors do not express envelope protein, the skilled artisan would have had no reason to believe that receptor interference would play any role in preventing superinfection of the cells. Thus, to achieve a greater level of protein expression, the skilled artisan would have been motivated to perform a serial transduction protocol until a sufficient number of integrant was achieved to lead to the desired level of protein production. Therefore it would have been obvious to one of ordinary skill in the art to combine the teachings of Inaba with those of Mathor in order to achieve a greater level of protein production. Indeed, the skilled artisan would have found it obvious to repeat the4 infection protocols as many times as necessary to achieve the desired level of protein production, which could easily be in the range of 50 pg/cell/day.

26. Claims 1-21, 27-34, and 41-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mathor and Inaba in view of Clontech (CLONTECHniques, 4/1999 pages 8-9, newly cited) and further in view of Hoatlin (J. Mol. Med. 73:113-120 (1995), newly cited). As discussed above, Mathor and Inaba combine to teach a method for transducing cells with a retroviral construct where repeated exposure of the cells to the retroviral construct is used to lead to increased numbers of integrated retroviral vectors and increased levels of protein expression, Mathor and Inaba do not teach the use of retroviral vectors which have been produced in packaging cells engineered to express gag and pol, but requiring transfection of an envelope protein, which can be VSV-G. Additionally, Mathor and Inaba do not teach that the retroviral vector can be a lentiviral vector.

27. Clontech teaches the technique of producing a retroviral vector that has been pseudotyped with VSV-G (whole article). Indeed, the VSV-G retrovirus is produced by cotransfecting GP-293 cells, which have been engineered to express gag and pol from MoMLV, with the retroviral

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vector and a vector encoding VSV-G. One would have been motivated to use a VSV-G pseudotyped retrovirus as taught by Clontech in the retroviral transduction method of Mathor and Inaba because as Mathor states high level of protein expression is desired, and Clontech teaches that VSV-G retroviruses can be concentrated using ultracentrifugation thus increasing the viral titer, ultimately leading to higher level expression of the gene of interest, the desired outcome of Mathor and Inaba. The skilled artisan would have been motivated to further transduce the host cells comprising multiple integrated vectors with the VSV-G retrovirus because the pseudotyped virus, having a totally different envelope protein absolutely can be subject to the remote possibility of receptor interference, since the VSV-G protein uses a lipid receptor, while the ecotropic and amphotropic packaged retroviruses recognize protein receptors.

28. Further supporting this motivation, Hoatlin teaches (see the Abstract) that retroviruses bearing different receptors, specifically amphotropic and ecotropic in the case of Hoatlin, which can repeatedly infect cells as no interference exists between the amphotropic and ecotropic receptors. This so-called ping-pong technique leads to high-level expression and multiple integrations. Thus by retransducing with VSV-G pseudotyped retrovirus, one would have essentially been mimicking a single ping-pong cycle, leading to even higher level expression than achieved with simple repeated infections. Therefor, it would have been obvious to one of skill in the art to combine the teachings of Clontech and Hoatlin with those of Mathor and Inaba to achieve even higher-level expression of the gene of interest.

29. Claims 1-14, 16-21, 25, 27-34, and 41-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mathor and Inaba as applied to claims 1-11, 18-21, 27-34, and 41-42 above, and further in view of Naldini (Science 272: 263-267 (1996), newly cited). Mathor and Inaba, do

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not disclose the use of a lentiviral vector or methods where the retrovirus is produced from packaging cells transfected with an envelope gene and a vector plasmid, or where the packaging cells can express gag and pol proteins and the envelop can be VSV-G. Naldini discloses (see particularly Figure 1) a pseudotyped lentiviral vector that bears VSV-G as the retroviral receptor. The packaging cells express gag and pol upon transfection of the packaging construct, and the retroviral vector (transfer vector) is transfected with the VSV-G encoding env-encoding plasmids. One would have been motivated to use the lentiviral vector of Naldini in the transduction methods because lentiviral vectors are particularly useful as they can “integrate into the genome of nonproliferating cells” (page 263, column 1, center of first paragraph). Motivation specifically for using the pseudotyped vector and for performing the additional step of claim 13 can be found in paragraphs 27-28. Therefore it would have been obvious to one of skill in the art to combine the teachings of Naldini with those of Mathor and Inaba to use a VSV-G pseudotyped lentiviral vector, because a VSV-G-expressing lentiviral vector would allow for infection of nondividing cells and high level expression of the protein of interest.

30. Claims 1-11, 18-24, 27-34, 39, and 41-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mathor and Inaba as applied to claims 1-11, 18-21, 27-34, and 41-42 above, and further in view of Primus and Deng (Biotechniques 25:274-279 (1998), newly cited). Mathor and Inaba do not teach of the retrovirus comprising two genes of interest, where the two genes are expressed in a bicistronic fashion and the two genes comprise the heavy and light chains of immunoglobulin which may be IgG. As discussed above in paragraphs 19 and 20 Primus discloses a method of introducing a monoclonal IgG2a antibody into a cell whereby first the light chain then the heavy chain are transduced retrovirally. Primus does not disclose expression of the

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two chains of the antibody in a single bicistronic vector. Deng discloses (see particularly Figure 2) vectors for the bicistronic expression using an internal ribosome entry site (IRES). The use of IRES-containing vectors was not yet widely practiced at the time of the Primus publication, but as the 1990s progressed this technique became much more common. Therefore, to simplify the process of producing cells that would express antibodies, the skilled artisan would have been motivated to combine the two separate vectors of Primus into a single IRES vector as taught by Deng. To achieve high level expression of that bicistronically-expressed antibody vector of Primus and Deng, the skilled artisan would have been motivated to use the serial transduction methods of Mathor and Inaba with the bicistronic vector of Primus and Deng. Therefore, it would have been obvious to one of skill in the art to combine the teachings of Mathor and Inaba with those of Primus and Deng to achieve multiple integrations of the bicistronic retroviral vector and consequently high-level expression of the antibody.

31. Claims 1-11, 18-21, 26-38, and 41-42 rejected under 35 U.S.C. 103(a) as being unpatentable over Mathor and Inaba as applied to claims 1-11, 18-21, 27-34, and 41-42 above, and further in view of Schroder. Mathor and Inaba together disclose a method for transducing host cells using a method of repeated transduction, as described above in paragraphs 24-25. Mathor and Inaba do not disclose the inclusion of an amplifiable marker, which can be DHFR, in the retroviral vector with the method also comprising growing the cells under conditions including for example methotrexate to get amplification of the integrated retroviral vectors. Mathor and Inaba additionally do not disclose using CHO cells as the host cells for retroviral transduction.

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32. Schroder discloses (see Abstract, Introduction, and Table I) the amplification of hATIII expression in CHO cells through DHFR-mediated amplification of the genes by treating with methotrexate. The skilled artisan would have been motivated to include an amplifiable marker such as DHFR, as taught by Schroder, in the retrovirus of Mathor and Inaba for the increased production of the protein of interest because gene amplification is known to be an effective mode of increasing production of a protein of interest. The skilled artisan would have been motivated to use CHO cells, as taught by Schroder, in the protein production methods of Mathor and Inaba because CHO cells are known to be an excellent model cell line for the high level production of a protein of interest. Therefore, it would have been obvious to one of ordinary skill in the art to combine the teaching so Schroder with those of Mathor and Inaba in order to achieve maximal protein production.

33. Claims 1-11, 18-21, 27-34, and 40-42 rejected under 35 U.S.C. 103(a) as being unpatentable over Mathor and Inaba as applied to claims 1-11, 18-21, 27-34, and 41-42 above, and further in view of Dranoff. Mathor and Inaba disclose a method of transducing cells with retroviral vectors where a multiple transduction method is used. Mathor and Inaba do not disclose transduction with two different vectors encoding two different genes. Dranoff discloses (see Example 8) the retroviral transduction of multiple genes into tumor cells. One would have been motivated to use the repeated transduction methods of Mathor and Inaba with the multiple cytokine gene expressing vectors of Dranoff because higher level expression of the various cytokine genes would be desirable for enhancing the efficacy of the "tumor vaccines" of Dranoff, potentially so fewer transduced tumor cells would be necessary for efficient "vaccination". Thus, it would have been obvious to one of skill in the art to express multiple

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genes in a host cell, as taught by Dranoff, using the repeated transduction methods of Mathor and Inaba.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Kozak and Bestwick disclose the so-called ping-pong method of retroviral infection which leads to multiple integrations of the retroviral vector and high levels of protein production. Abbas discloses the different antibody isotypes. McGeady and Levine are exemplary of different cell types which are useful as host cells.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick S. Riggins whose telephone number is (571) 272-6102. The examiner can normally be reached on M-F 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patrick Riggins, Ph.D.
Examiner
Art Unit 1636



JAMES KETTER
PRIMARY EXAMINER